TOGETHER

WE

ADVANCE SCIENCE TO BENEFIT HUMANKIND

IMPACT DISCOVER PROTECT ACHIEVE CARE REALIZE

THE WISTAR INSTITUTE 2008 ANNUAL REPORT
IMPACT the well-being of those suffering from melanoma and other forms of cancer.

DISCOVER new targets for potential prevention and treatment of cancer, infectious diseases, and other illnesses.

PROTECT the lives of people everywhere by developing vaccines for influenza, rabies, and other diseases.

ACHIEVE the goal of understanding what drives cancer and how we can prevent it.

CARE deeply about improving the health of men, women, and children.

REALIZE the goal of translating basic science into discoveries that will change the world.
“Team science is the new paradigm. Bringing researchers who specialize in diverse disciplines together around a common question of science, giving them the tools and resources they need to find answers—this is the new approach to understanding the basic biological processes fundamental to life and health.”
We’ve all heard the saying, *the whole is greater than the sum of its parts*. Nowhere does this hold more true than at modern biomedical research institutions like The Wistar Institute. Team science is the new paradigm. Bringing researchers who specialize in diverse disciplines together around a common question of science, giving them the tools and resources they need to find answers—this is the new approach.

Team science is evolving as the research community begins to tease apart and analyze the wealth of clues about human biology revealed by the first complete sequencing of the human genome in 2003. Inspired to explore the next frontier and powered by high-end instrumentation, Wistar researchers and their colleagues around the globe now study human biology—what drives growth, development, health, and disease—at the molecular level.

As a result, new scientific disciplines have emerged. Researchers once worked individually as chemists, biologists, and geneticists to study discrete aspects of the biological processes underlying disease. Today, cooperative teams of scientists explore the disciplines of molecular biology, genomics, and systems biology to learn how these aspects work together. Each brings a unique perspective to the task; together they mine the trove of information about human biology now at our fingertips.

While the moniker “team science” may be new, at Wistar the concept is as enduring as the very foundation on which our Institute is built. Our size and culture of collegiality have historically fostered the multidisciplinary interactions synonymous with team science. A relatively small, collaborative faculty sharing state-of-the-art facilities in pursuit of 21st century science generates tremendous synergy—those bright-light moments of discovery that advance the field and lead to progress toward improving public health.

As I write this letter, we are experiencing a global pandemic of the H1N1 influenza virus—part swine, part human, part avian—to which humans have limited immunity. As you’ll read in these pages, team science at Wistar has produced two prototypes for a universal flu vaccine that could, with further development, protect all of us against similar pandemics in the future.

Wistar team science is also yielding clues about the nature of human stem cells and their role in cancer. And Wistar teams are developing molecular compounds capable of inhibiting the genes and proteins involved in cancer, pointing the way toward the future development of promising new preventions and therapies.

You’ll also see that Wistar science is a catalyst for fruitful extramural partnerships and collaborations to bring our discoveries from our lab benches ultimately to patients’ bedsides.

None of this would be possible without our many friends and generous supporters who have embraced the Wistar mission and made it their own. We are proud and grateful to have each of you on our team as, together, we advance science to benefit humankind.

Russel E. Kaufman, M.D.
*President and CEO*
# TABLE of CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FULL FRONTAL ATTACK ON SKIN CANCER</td>
<td>4</td>
</tr>
<tr>
<td>molecular and cellular oncogenesis</td>
<td></td>
</tr>
<tr>
<td>BENCH BEFORE BEDSIDE</td>
<td>8</td>
</tr>
<tr>
<td>molecular screening facility</td>
<td></td>
</tr>
<tr>
<td>PURSUING A UNIVERSAL FLU VACCINE</td>
<td>10</td>
</tr>
<tr>
<td>immunology</td>
<td></td>
</tr>
<tr>
<td>WISTAR IN THE NEWS</td>
<td>14</td>
</tr>
<tr>
<td>MESSAGE FROM THE CHAIR</td>
<td>18</td>
</tr>
<tr>
<td>THE YEAR IN REVIEW</td>
<td>19</td>
</tr>
<tr>
<td>wistar at a glance</td>
<td></td>
</tr>
<tr>
<td>CUMULATIVE GIVING</td>
<td>20</td>
</tr>
<tr>
<td>ANNUAL GIVING</td>
<td>23</td>
</tr>
<tr>
<td>IN HONOR OF</td>
<td>26</td>
</tr>
<tr>
<td>IN MEMORY OF</td>
<td>27</td>
</tr>
<tr>
<td>SCIENTIFIC AND ADMINISTRATIVE STAFF</td>
<td>30</td>
</tr>
<tr>
<td>BOARD OF TRUSTEES</td>
<td>32</td>
</tr>
</tbody>
</table>
Every year, doctors will diagnose 60,000 people in the United States with melanoma, one of the most common and aggressive forms of cancer. Highly treatable when detected early, the disease can be fatal if left unchecked. Of those diagnosed, 8,000 eventually will die from the disease, 85 percent within five years of diagnosis.

Meenhard Herlyn, D.V.M., D.Sc., has dedicated his life to changing these statistics and improving the outlook for people at risk of developing melanoma and those diagnosed with the disease. Chair of Wistar’s Molecular and Cellular Oncogenesis Program, Herlyn runs one of the largest melanoma research programs outside of the National Institutes of Health and has studied the cancer for more than two decades. He also understands the best weapon against melanoma or any type of cancer is a full frontal attack by a multidisciplinary team of experts.

Herlyn leads such a team, supported in large part by Wistar’s prestigious SPORE (Specialized Program of Research Excellence) grant in skin cancer, a National Cancer Institute—funded program for the prevention, diagnosis, and treatment of melanoma. One of only five such awards nationwide, the SPORE brings together experts from Wistar and the University of Pennsylvania (Penn). Together, they develop new tools for fighting the deadly skin cancer and treatments for patients suffering from it.

The SPORE team is comprised of tumor biologists, oncologists, pathologists, geneticists, epidemiologists, immunologists, surgeons, and dermatologists. Each brings specialized input to the research and enables the team to target melanoma from every possible angle. The large-scale project takes discoveries from the lab bench, where Wistar’s scientists pursue early-stage biomedical research, to the patient’s bedside, where Penn’s physicians conduct clinical trials of potential new therapies. And in the continuous cycle of translational scientific inquiry, the clinicians bring patient data and knowledge gleaned in practice back to their colleagues at the research bench, where it informs new strategies and paths of discovery.

"As a team, we are able to set more ambitious goals and develop the disease models necessary to meet them," says Herlyn. "In the end, teamwork across many disciplines means a greater impact against melanoma for people around the world."

Since receiving the first SPORE in 2001, the team has made great advances in our understanding of melanoma. By profiling tumors at the molecular level, the researchers have identified markers that help clinicians diagnose the disease earlier, when the potential for cure is highest, more accurately assess an individual’s risk, and treat melanoma more effectively, based on a patient’s own genetic makeup.
Our SPORE was initiated in 2001 with a major emphasis on therapy and disease outcome prediction.
SORE projects have shed light on how the cancer metastasizes and the role melanoma stem cells—first identified by Herlyn in 2005 and commonly believed to be the starting point for cancer—play in the disease. The next step is to find ways to destroy these self-renewing tumor stem cells, which often elude standard treatments. Destroying them would, essentially, stop cancer growth in its tracks.

Perhaps most promising, the SORE investigators have tested a new generation of drugs that could literally change the standard of treatment for melanoma. Herlyn’s lab has long explored molecular signaling pathways—the chemical “conversations” between skin cells that normally maintain order in cell division and proliferation but can lead to melanoma when disrupted. Collaborative studies of these signaling pathways led to the development and early-phase clinical testing of a drug that targets BRAF, a mutant gene expressed in 65 percent of melanoma tumors, inhibiting its role in cancer and getting the “conversation” back on track. Herlyn is optimistic about the success of the approach, and the team plans to expand the project to target other signaling molecules.

“As a result of teamwork,” Herlyn believes, “in the near future, we can think of saving the lives of nearly every patient with melanoma.”

Herlyn has dedicated more than two decades to studying melanoma and runs one of the largest melanoma research programs outside of the National Institutes of Health.
Herlyn knows the science and statistics behind melanoma, but he had studied the cancer for 20 years before actually putting a human face to the disease. Then he met Noreen O’Neill, a vibrant young Philadelphian diagnosed with malignant melanoma in 1998.

Never content to sit on the sidelines despite her disease, O’Neill wanted to raise money for melanoma research. Finding no organizations focused specifically on melanoma, she started her own and enlisted Herlyn’s help.

Founded in 1999, the Noreen O’Neill Foundation for Melanoma Research (named after her death in 2000) advances the mission of raising awareness about melanoma and funding research toward the prevention, early detection, and treatment of the disease.

“A patient dealing with the day-to-day reality of cancer, my sister also had a very keen long-term view,” says Kate O’Neill, a member of the foundation’s board. “She knew that research is the key to improving treatment and eventually finding a cure.”

Since 1999, the foundation has given more than $230,000 to fund Wistar’s melanoma research programs.

“Noreen leaves a wonderful legacy,” says Herlyn, a foundation board member. “She put a face to our work, reminding us that we ultimately serve people. And her foundation provides the financial support we need to keep learning, so that fewer will suffer from melanoma.”
Wistar’s promise to the world is that discoveries made in its laboratories today will lead to tomorrow’s cures for human disease. With wide-ranging expertise in gene expression and regulation, immunology, and molecular and cellular oncogenesis, Institute researchers collaborate to understand the basic biology of cancer; HIV, influenza, and other viruses; heart disease; and many other serious health conditions. To advance Wistar’s public health mission, translating these biomedical discoveries into therapies and preventive vaccines is crucial to their work. In December, Wistar expanded its capability to move basic science discoveries from the laboratory onto the path toward future therapies for patients when it opened a $1.1 million Molecular Screening Facility at the Institute.

Much like finding a needle in a haystack, the earliest stages of the drug-development process can be slow and tedious. Identifying the genetic expression of a disease-causing protein and defining its structure are first steps, and ones at which Wistar scientists are international leaders. Then the search is on for a chemical compound, among hundreds of thousands, that, like a key in a lock, fits the protein’s structure and alters its function. To be a good candidate for potential drug development, the compound must be highly specific to its target in order to spare healthy tissue and avoid side effects for patients farther down the road.

Wistar’s new Molecular Screening Facility enables scientists to screen vast quantities, or “libraries,” of compounds quickly and accurately against their targets. Using robotic technology, the facility’s scientific staff work closely with their Wistar colleagues to try to find “hits” that inhibit the function of the target protein. These tests are designed to visualize and quantify this inhibitory effect at the molecular level and to identify the “needle in the haystack” that can be further studied and developed into the next generation of drug candidates.

"Wistar has always pushed the boundaries of science with research that broadens our understanding of how disease affects the human body," says Paul M. Lieberman, Ph.D., professor in the Gene Expression and Regulation Program and scientific director of the Molecular Screening Facility. "This new facility will help our scientists take their discoveries steps further, into the world of prevention and treatment."

The facility supports important cross-disciplinary teamwork among Wistar’s scientists. For example, Ronen Marmorstein, Ph.D., leader of Wistar’s Gene Expression and Regulation Program, and Meenhard Herlyn, D.V.M., D.Sc., leader of Wistar’s Molecular and Cellular Oncogenesis Program, are using the facility to explore potential melanoma therapies.

Marmorstein recently developed a novel enzyme inhibitor able to block the function of molecular signaling proteins called phosphatidylinositol-3-kinases (PI3Ks), mutations of which are well known to cause melanoma and other cancers. (See page 17.) Using small molecule screening, Marmorstein
PARTNER FOR DISCOVERY

The Molecular Screening Facility marks a new partnership between Wistar, Universit Lankenau Institute for Medical Research, building the capabilities of all three to trans new therapies. Wistar scientists will identify and refine targets and inhibitors in the f Lankenau; University of the Sciences’ researchers lend the medicinal chemistry and pl the discoveries into drug candidates ready for pre-clinical and ultimately, with furthe

SCRENNING THE TARGETS

A cancer-causing protein is placed in wells in hundreds of plastic plates, which are fed into sophisticated robotic machinery along with plates containing a “library” of thousands of chemical compounds to be tested. The equipment combines each test compound with the protein.

IDENTIFYING THE HITS

By studying the effects, scientists can identify “hits,” or highly specific compounds that inhibit the function of the cancer-causing protein, narrowing the scope for potential drug development.

first identified a “hit” molecule, and then with x-ray crystallography defined its structure bound to PI3K. Next, in a process called structure-guided optimization, Marmorstein refined this inhibitor to better target PI3K’s molecular signaling pathway. Herlyn then tested it in lab cultures of human melanoma and found it inhibited the growth of melanoma cancer cells.

Marmorstein is also working with Hildegund C.J. Ertl, M.D., leader of Wistar’s Immunology Program, to develop a therapy for human papillomavirus (HPV). A fairly common sexually transmitted virus, HPV infection increases the risk of developing cervical cancer, the second-leading cause of cancer-related deaths in women worldwide. Marmorstein is screening libraries of small molecules in the Molecular Screening Facility that would inhibit the oncogenic activity of the viral oncoproteins E7 and E6, which promote the development of cervical cancer. Such molecules would complement the therapeutic HPV vaccines that Ertl is developing. Although two vaccines have been approved for the prevention of HPV, Ertl and Marmorstein’s approach would be the first treatment for those who have already contracted HPV—and potentially a lifesaver for women everywhere.
of the Sciences in Philadelphia, and the
ate basic science discoveries into potential
ility using chemical libraries provided by
armacology expertise necessary to develop
refinement, clinical testing in humans.

Santosh Hodawadekar

REFINING THE HITS
On a more specialized machine, scientists closely study the
"hits" in order to further refine them into promising lead
compounds for drug development.

DANIEL AND FLORENCE GREEN

Daniel B. Green knows that individual donors have the power to save lives.
Ten years ago, Green’s daughter-in-law was an active fundraiser for cancer
research projects at the University of California, Los Angeles (UCLA) that
were not far enough advanced to qualify for government funding. In a twist
of fate, her husband, Green’s son, was diagnosed with leukemia and
received treatment at UCLA, where his physicians placed him on an experi-
mental drug protocol. A researcher whom Green’s daughter-in-law had
helped fund had developed the protocol. Today, Green’s son is alive and
thriving. Without early-stage funding, the treatment that eventually saved his
life would not have been possible.

Green tells this story to anyone who questions the efficacy of supporting
basic biomedical research. “Investing in research brings a lifetime of
fulfillment,” he says. “I go to sleep every night knowing that my support
may someday help cure cancer for good. The potential to change lives
forever is huge and exciting.”

When Green, trustee emeritus of the Lankenau Hospital Foundation
Board, learned of Wistar’s desire to build a molecular screening facility, he
recognized an opportunity to make a real difference. A generous gift from
the Daniel B. and Florence E. Green Foundation to Wistar helped make the
facility a reality.

Green also fostered the partnership with the Lankenau Institute for
Medical Research. He says, “Wistar’s facility is a wonderful example of
institutions cooperating for the greater good of the people they ultimately
aim to serve.”
“Having a screening facility onsite offers our scientists the opportunity to engage in multidisciplinary discovery research and take observations from their laboratories to the point of defining novel therapeutic strategies. It allows them to expand their research programs in creative directions and will help Wistar pursue its mission to improve human health by recruiting the best and brightest to our labs.”

David Schultz, Ph.D. | Molecular Screening Facility Director
PURSUING A UNIVERSAL FLU VACCINE

immunology

Come autumn, as leaves change color and temperatures cool, many of us begin lining up for our annual influenza virus (flu) vaccination. Because the virus mutates over time, last year’s vaccine may not protect against this year’s flu, making vaccination a necessary yearly ritual. Flu shot reminders, especially for the elderly and other vulnerable populations, become the mantra of doctors throughout the flu season.

Researchers in The Wistar Institute Vaccine Center are pursuing a universal flu vaccine that would eliminate the need for regular vaccinations and provide better protection not only for those at risk, but for all of us. Supported by a $4.2 million Commonwealth Universal Research Enhancement (CURE) grant from the Pennsylvania Department of Health, the Center is working with noted scientists from Temple University, Children’s Hospital of Philadelphia (CHOP), the University of Pennsylvania, and Penn’s School of Veterinary Medicine (Penn Vet) on a new approach.

Current flu vaccines target two prominent protein molecules on the surface of the virus. Every year, these proteins mutate to varying degrees, reducing the usefulness of the antibodies produced to fight the previous year’s virus. The Wistar vaccine team aims to create a novel vaccine directed against viral proteins that are less prone to mutation than the two proteins targeted by current vaccines. They will also develop a “cocktail” of antibodies against the flu virus to be given as an early treatment for flu infection.

Wistar currently has two prototypes in early-stage testing in mice: a peptide vaccine and a viral vector vaccine, which may be used in sequence for a one-two boost to the immune system. While many questions remain and much work lies ahead, the team’s promising approach could eventually eliminate the need for annual visits to the doctor for flu shots, provide better protection against infection, and guard against a pandemic, such as avian flu, which occurs when a new strain of flu emerges that is both deadly and highly contagious.

Each institution contributes a very specific expertise, without which the project could not succeed. CHOP and Penn Vet provide blood and serum samples from flu-infected children and others who have been exposed to the avian flu virus. Analysis of antibody response in the samples aids Wistar researchers in designing vaccines by “setting the bar” for the minimum immune response they must induce to achieve protection. Temple designed and manufactured one of the vaccine components.
Annually in the United States, 200,000 people are hospitalized and 40,000 people die from the flu. A universal flu vaccine has the potential to save the U.S. healthcare system $10 billion a year; the value of lives saved would be immeasurable.
“Twenty years ago, a project such as this would have been possible only in the pharmaceutical industry, which had the money and capability for large-scale research,” says Hildegund C.J. Ertl, M.D., director of the Wistar Vaccine Center. “Today, as industry cuts research budgets, teams such as ours increasingly carry the research mantle. Disease protection and cures come only when we work together to a common end.”

As part of the project, Wistar is also training future generations of biomedical scientists through a partnership with Cheney University of Pennsylvania. Cheney faculty members work in the Wistar Vaccine Center throughout the year, and Cheney students spend eight weeks each summer in the Center learning about vaccine research through hands-on experience and lectures. Working side by side with Wistar researchers, these future scientists make real contributions to a team that may well make “flu season” a thing of the past.

“Imagine the tremendous, beneficial impact a universal flu vaccine would have on the health of people living in Pennsylvania. By funding leading-edge flu vaccine research at The Wistar Institute, the Commonwealth is investing in the future health of its own citizens and, potentially, all humankind. I consider that a wise investment.”

Edward G. Rendell | Governor, Commonwealth of Pennsylvania
SAVING LIVES, ONE VACCINE AT A TIME

One of the greatest public health advances ever, vaccines save millions of lives every year. Wistar has a long, distinguished record of developing vaccines that have prevented life-threatening diseases and eradicated major public health threats in countries around the globe.

Wistar scientists have created vaccines for rabies, rubella (otherwise known as German measles), and rotavirus, one of the most common causes of severe dehydrating diarrhea in infants and young children. In addition to the universal flu vaccine, Wistar scientists are pursuing vaccines for HIV, malaria, and hepatitis C, among others.

Committed to improving health for people everywhere, the scientists who work on these vaccines also partner with funders and global public health agencies to bring the vaccines—either in their final form or during widespread clinical trials—to developing nations, where thousands of people die or suffer every day from diseases that are now rare in the United States thanks to regular access to Wistar vaccines.
Landmark Study Opens Door to New Cancer, Aging Treatments

Wistar researchers have deciphered the structure of the active region of telomerase, an enzyme that plays a major role in the development of nearly all cancers. The landmark achievement opens the door to the creation of new, broadly effective cancer drugs and anti-aging therapies.

Researchers have attempted for more than a decade to find drugs that shut down telomerase, widely considered the primary target for the development of new cancer treatments. A lack of information about the enzyme’s structure has hampered their efforts.

The findings, published in August’s Nature, should help researchers design effective telomerase inhibitors, says Emmanuel Skordalakes, Ph.D., assistant professor in Wistar’s Gene Expression and Regulation Program, who led the study.

"Telomerase is an ideal target for chemotherapy because it is active in almost all human tumors, but inactive in most normal cells," Skordalakes says. "That means a drug that deactivates telomerase would likely work against all cancers, with few side effects."

The study elucidates the active region of telomerase and provides the first full-length view of the telomerase molecule’s critical protein component. It reveals surprising details, at the atomic level, of the enzyme’s configuration and how it works to replicate the ends of chromosomes—a process critical to both tumor development and the aging process.

In humans, telomerase adds multiple repeats of a short DNA sequence to the ends of chromosomes, known as telomeres, thus preventing damage and the loss of genetic information during cell division.

When telomerase is dormant, telomeres shorten each time a cell divides, leading eventually to genetic instability and cell death. By preserving chromosomes’ integrity, telomerase allows cells to continue living and dividing. The enzyme is active in cells that multiply frequently, such as embryonic stem cells, but is switched off almost entirely in normal adult cells to prevent the dangers of runaway cell proliferation.
Cancer cells, however, often regain the ability to activate telomerase, which has been implicated in 90 percent of human tumors. The enzyme permits cells to replicate indefinitely and achieve the cellular "immortality" that is the hallmark of cancer. Deactivating telomerase would stop tumor growth.

In addition, telomerase holds significant implications for the development of therapies to combat aging and age-related diseases. Finding ways to activate telomerase under controlled conditions and allow some cells to begin dividing again could result in healthier, younger-looking tissue that lives longer.

**Wistar Scientists Find Key to Keeping Killer T Cells in Prime Shape for Fighting Infection, Cancer**

Wistar Institute researchers have found multiple receptors on the outside of the body’s killer immune system cells that they believe can be selectively targeted to keep the cells in superb infection- and disease-fighting condition.

In a study published in November’s *Nature Immunology*, lead author E. John Wherry, Ph.D., an assistant professor in Wistar’s Immunology Program, describes the discovery of seven different T cell receptors that can tamp down immune responses during a prolonged battle with an infectious pathogen or against developing cancer.

Chronic over-stimulation of the immune system can lead to poor control of infections and cancer, so the results explain why these key immune cells gradually become "exhausted" and ineffective over time.

This knowledge presents great clinical opportunity. T cells have many weapons that control viral infection, most of which are disarmed when the cells become exhausted. Wherry believes it may now be possible to selectively rearm T cells while generally reinvigorating them.

Wherry, named by *Smithsonian* magazine as one of 37 American innovators under the age of 36 for his work on a universal flu vaccine (see pages 10-13), recently helped discover a single receptor involved in turning off T cells, but this new study shows that at least six more receptors can also restrain or negatively regulate immune responses.

A key finding is that these new receptors likely control different aspects of T cell responses, such as division or expansion, controlling viral replication, and local killing of infected cells versus secretion of long-range active antiviral proteins.

"We are starting to see a picture emerging of a really tunable array of inhibitory receptors expressed on T cells," Wherry says, "which suggests it may be possible to not only dramatically enhance antiviral or antitumor T cell responses but also to fine-tune which response to enhance in order to reverse T cell exhaustion and continue fighting an infection or disease."
Wistar Opens Center for Systems and Computational Biology

In March 2008, Wistar dedicated its new Center for Systems and Computational Biology. The Center, which houses high-powered computers and technologically advanced instruments, supports Wistar scientists in developing new tests for the early diagnosis of cancers and other diseases and new treatments. Using the Center’s technology, scientists can produce and process vast amounts of data at an unprecedented rate, a crucial ability for today’s team scientists.

Historically, researchers tended to focus on single genes, molecules, or small groups of molecules. Today’s emphasis is on systems biology, which focuses on the large-scale analysis of complex biological systems and takes a more open-ended approach to research. Instead of exhaustively studying the function of one gene, for example, a systems biologist might seek to identify all the genes or proteins involved in a particular biological function.

This approach depends upon technology and computation, which the Center provides. Supporting research efforts across the Institute’s programs, the Center will eventually provide 100 times greater computing and data storage capacity than was previously possible.

The Center is particularly valuable in bolstering Wistar’s programs in genomics and proteomics—the study of genes and proteins, respectively. The new facility’s technologically advanced equipment includes a gene sequencer that can rapidly sequence an entire genome, helping researchers to identify genetic changes that influence cancer, HIV/AIDS, cardiovascular disease, and other diseases.

Discovery of Novel Inhibitor of Human MicroRNA Points to New Avenue for Cancer Treatment

The first-time identification of a molecule that can regulate microRNAs (miRNAs)—short strands of RNA that play a vital role in gene expression and are closely associated with cancer—points the way to the development of a new generation of cancer drugs.

Wistar scientists identified a small molecule that blocks the pathway of a particular miRNA called miR-21, implicated in cancers of the brain, lung, colon, breast, and ovary. With further development, the molecule has the potential to boost patient response to existing chemotherapies and to become a stand-alone cancer drug.

The importance of miRNAs in regulating human development and disease is clear. While the human genome is thought to contain 800 to 1,000 miRNAs, only a few hundred have been described. Thus, miRNAs represent a largely unexplored class of targets for the development of therapeutics and diagnostics.

“This is a totally novel target,” says Qihong Huang, M.D., Ph.D., an assistant professor in Wistar’s Molecular and Cellular Oncogenesis Program and co-senior author of the study, published in September’s Angewandte Chemie. “It’s very understudied, but its potential is tremendous. Because miRNAs have the ability to shut down genes and prevent their expression, they may ultimately provide a target for therapies that are more selective than conventional chemotherapy drugs and have fewer side effects.”
Center director David W. Speicher, Ph.D., relies on the Center’s computer resources, analytical tools, and faculty expertise to analyze complex protein data. He and his team are identifying protein “biomarkers” shed by cancers into the blood in hopes of soon developing blood tests that can detect cancer early.

“The Center’s ability to analyze that data at a level previously unheard of is highly enabling,” says Speicher. “With these resources, we will accomplish things we couldn’t even conceive of a few years ago.”

**Novel Enzyme Inhibitor Paves Way for New Cancer Drugs**

Combining natural organic atoms with metal complexes, Wistar scientists have developed a new type of enzyme inhibitor capable of blocking a biochemical pathway that plays a key role in cancer development.

The research paves the way for new cancer treatments by damping the overactive enzyme activity that leads to uncontrolled tumor growth. In a study published in May’s *ACS Chemical Biology*, scientists show how small-molecule inhibitors can be designed to target a family of signaling proteins, called phosphatidyl-inositol-3-kinases, or PI3Ks.

“The PI3K pathway has been called the most mutated pathway in human cancer,” says Ronen Marmorstein, Ph.D., leader of Wistar’s Gene Expression and Regulation Program and senior author of the study.

PI3Ks are a family of lipid kinases—enzymes that transfer a phosphate group to an important signaling molecule in the cell called a lipid. They play a key role in a wide range of cellular functions. Kinases have been the focus of drug-development strategies for years, but the drugs often lack specificity. Such broad-spectrum agents, while potentially inhibiting the mutated PI3K pathway, may also inhibit other related kinases, inevitably causing unwanted side effects.

To overcome this hurdle, Marmorstein set out to create a lipid kinase inhibitor with greater specificity using a metal complex in its structure. He combined traditional organic compounds with the metal Ruthenium to create a novel scaffold, the platform on which the inhibitor was constructed.

By screening a library of chemical compounds, Marmorstein and colleagues identified a protein kinase inhibitor known as DW2. They then used X-ray crystallography to determine the three-dimensional structure of PI3K bound to DW2, using the structure as a “starting point” to fashion more effective PI3K inhibitors. Ultimately, they refined their inhibitor, called E5, and tested it against five different human protein kinases. The study showed E5 selectively targeted the PI3K lipid kinases.

With Professor Meenhard Herlyn, D.V.M., D.Sc., Marmorstein then tested the effectiveness of the agent using melanoma cell cultures. Results showed that E5 inhibited the growth of melanoma cells and prevented melanoma cell invasion.

**Ronen Marmorstein, Ph.D. (left)**
At The Wistar Institute, teams of the world’s best and brightest scientists work together to ensure a healthier future for us all. They are making tremendous progress in understanding the basic human biology underlying disease, which is the first step to developing better, more effective therapies. This is a particular area of strength for Wistar. Its scientists are world leaders in discovering molecular compounds with outstanding potential for further development into new drugs for cancer and other diseases.

Their success is due in great part to their collaborative "team science." Wistar scientists together approach common research problems, bringing their own unique and diverse perspectives and specialized expertise. Supported by philanthropy and other funding, and working in state-of-the-art facilities with the latest tools and technologies, they advance science and make great progress toward improving public health.

In recent years, the Institute has made a $15 million investment in new scientific facilities and technologies to support this critical research. Philanthropy, including a generous gift from Wistar friends Daniel and Florence Green, enabled the construction of a new Molecular Screening Facility where researchers are already beginning to identify promising compounds for further development into new drugs which would save lives.

Without the commitment of people like the Greens and Wistar’s many generous supporters, research progress would stall. Creative energy and collaboration spark promising research ideas, but they must be nurtured by philanthropy or many projects simply will not get off the ground.

While not all of us are scientists, we all are vital participants in team science at Wistar. Those of us who care deeply about realizing Wistar’s mission can be proud of our contribution.

I thank all of you who support The Wistar Institute as we pursue today’s discoveries and tomorrow’s cures. If you have not yet joined our team, I invite you to do so.

Brian H. Dovey
Chair, Board of Trustees
STAFF

Total number of employees 434
Number of laboratories 30
Number of postdoctoral fellows 62
Number of predoctoral trainees 23
Number of visiting scientists 24
Number of countries of origin represented 32
(Algeria, Argentina, Australia, Austria, Brazil, Canada, China, Croatia, Cuba, France, Germany, Ghana, Greece, Hungary, Iceland, India, Ireland, Italy, Japan, Kenya, Korea, Norway, Peru, Poland, Romania, Russia, Singapore, Taiwan, Trinidad, United Kingdom, United States, Vietnam)

U.S. PATENTS ISSUED


Method of Delivering Genes to the Central Nervous System of a Mammal, Nigel W. Fraser, U.S. Patent No. 7,402,308

RESEARCH CENTERS

The Albert R. Taxin Brain Tumor Research Center
The Center for Chemical Biology and Translational Medicine
The Center for Systems and Computational Biology
The Robert A. Fox Structural Biology Center
The Wistar Institute Cancer Center
The Wistar Institute Vaccine Center

SHARED FACILITIES

Animal Facility
Bioinformatics Facility
Flow Cytometry Facility
Genomics Facility
Histotechnology Facility
Hybridoma Facility
Microscopy Facility
Molecular Screening Facility
Mouse Genetics Facility
Protein Expression Facility
Proteomics Facility
Research Supply Facility

THE YEAR IN REVIEW

Wistar at a Glance

STAFF

Total number of employees 434
Number of laboratories 30
Number of postdoctoral fellows 62
Number of predoctoral trainees 23
Number of visiting scientists 24
Number of countries of origin represented 32
(Algeria, Argentina, Australia, Austria, Brazil, Canada, China, Croatia, Cuba, France, Germany, Ghana, Greece, Hungary, Iceland, India, Ireland, Italy, Japan, Kenya, Korea, Norway, Peru, Poland, Romania, Russia, Singapore, Taiwan, Trinidad, United Kingdom, United States, Vietnam)

U.S. PATENTS ISSUED


Method of Delivering Genes to the Central Nervous System of a Mammal, Nigel W. Fraser, U.S. Patent No. 7,402,308

RESEARCH CENTERS

The Albert R. Taxin Brain Tumor Research Center
The Center for Chemical Biology and Translational Medicine
The Center for Systems and Computational Biology
The Robert A. Fox Structural Biology Center
The Wistar Institute Cancer Center
The Wistar Institute Vaccine Center

SHARED FACILITIES

Animal Facility
Bioinformatics Facility
Flow Cytometry Facility
Genomics Facility
Histotechnology Facility
Hybridoma Facility
Microscopy Facility
Molecular Screening Facility
Mouse Genetics Facility
Protein Expression Facility
Proteomics Facility
Research Supply Facility

SOURCES OF FUNDS

Federal grant funding 28,602,000 58%
Foundation and other private funding 4,239,000 9%
State funding (Commonwealth of Pennsylvania) 2,782,000 6%
Corporate-sponsored research 372,000 1%
Unrestricted contributions 1,825,000 4%
Technology transfer 10,758,000 22%
TOTAL 48,578,000 100%

USES OF FUNDS

Direct research 32,233,000 42%
Administration and laboratory services 8,126,000 11%
Operation and maintenance of plant 5,921,000 8%
Library operation 396,000 1%
Depreciation of capital assets 3,681,000 5%
Investment losses 25,372,000 33%
TOTAL 75,729,000 100%
CUMULATIVE GIVING

**President’s Council** ($1,000,000.00 +)
- American Cancer Society
- Arthritis Foundation
- Commonwealth of Pennsylvania
- Mr. and Mrs. Harold M. Davis
- Mr. and Mrs. Robert A. Fox
- Dr. Herbert Kean and The Honorable Joyce Kean
- F. M. Kirby Foundation, Inc.
- G. Harold & Leila Y. Mathers Charitable Foundation
- The Pew Charitable Trusts
- Philadelphia Health Care Trust
- W. W. Smith Charitable Trust

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- The Breast Cancer Research Foundation
- Mr. Ira Brind
- The Ellison Medical Foundation
- Edward Mallinckrodt, Jr. Foundation
- The Elsa U. Pardee Foundation
- The Philadelphia Foundation
- Fannie E. Rippel Foundation
- The V Foundation for Cancer Research

**Centennial Society** ($100,000.00 +)
- Accelerate Brain Cancer Cure
- Dr. Miriam & Sheldon G. Adelson Charitable Trust
- American Health Assistance Foundation
- The Arcadia Foundation
- Arnold and Mabel Beckman Foundation
- Mr. and Mrs. Vincent G. Bell, Jr.
- Mr. and Mrs. Ian J. Berg
- Mr. and Mrs. Robert S. Blank
- Brain Tumor Society
- Breast Cancer Alliance, Inc.
- The Campbell Foundation
- Cancer Research and Prevention Foundation
- Cancer Research Institute
- CLAWS Foundation
- Concern Foundation for Cancer Research
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- First Union National Bank
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*Deceased*
William (Bill) Wikoff Smith was a man of many talents and varied interests. An army pilot and successful business leader, he made his mark as president of the Kewanee Oil Company. He was also an avid photographer, sailor, and model ship builder. Nothing, however, was more important to Smith than helping people. Throughout his life, he maintained a steadfast commitment to making social responsibility a part of his daily life.

That noble commitment endures in the form of the W.W. Smith Charitable Trust, established in 1978, according to the terms of Smith’s lasting will, to help Philadelphia’s most vulnerable residents. Since then, the Trust has provided for the most basic and fundamental needs of people in the Philadelphia region through its support of basic biomedical research; scholarships and financial aid; and food, clothing, and shelter for the young and old.

Since 1979, the Trust has supported Wistar researchers, many at the beginning stages of their research. Over the years, it has funded more than 30 scientists and given more than $4 million to support cancer, cardiology, HIV, and basic research across all Wistar programs.

Many Wistar scientists credit the Trust’s early support of their research as the foundation from which they were able to secure future grants from national and international funding agencies. “Support from the W.W. Smith Trust enabled me to conduct key research on pediatric brain cancer that led to a generous grant from the American Cancer Society,” says Nadia Dahmane, Ph.D., assistant professor in the Molecular and Cellular Oncogenesis Program and a member of Wistar’s Albert R. Taxin Brain Tumor Research Center.

Dahmane is making important discoveries about the origins of medulloblastoma, the most common and malignant type of pediatric brain cancer. She and her team discovered the novel znf238 gene that controls the Sonic hedgehog (SHH) signaling pathway, which plays a key role in cell division and, when the process goes awry, can lead to medulloblastoma. They are studying znf238’s relationship to SHH and its potential ability to suppress tumor growth and development.

“The Trust made these discoveries possible,” says Dahmane. “Its support helped us move one step closer to curing medulloblastoma.”
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The Wistar Heritage Society recognizes the foresight and generosity of individuals who elect to perpetuate their support of biomedical research by including the Institute in their wills or estate plans. Membership is a partnership for life that offers the promise for discovery of new treatments and cures for cancer and other diseases.

Questions regarding membership in the Wistar Heritage Society should be directed to Wistar’s Development Office at (215) 898-3930. Members as of April 11, 2009 are:

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Howard S. Turner, Ph.D.

1 Representative of the Academy of Natural Sciences elected according to the terms of the Deeds of Trust.
2 Resigned March 2009.
3 Resigned December 2008.
4 Effective January 2009.
5 Wistar family representative, elected according to the terms of the Deeds of Trust.
6 Deceased October 2008.

The Leadership Council of The Wistar Institute is a group of community leaders who complement the Board of Trustees in helping the Institute forge new relationships and plan for its future.
TODAY’S DISCOVERIES
TOMORROW’S CURES

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The Wistar Institute’s 2008 Annual Report was produced by the Office of Communications.

Staci Vernick Goldberg, Director of Communications
Lee Christine Shurtz, Communications Assistant
Writing: Sacha Adorno, Staci Vernick Goldberg
Design: SK Designworks, Inc.
Photography: Tommy Leonardi
Supplemental Photography: Frederick S. Keeney, James E. Hayden
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Published May 2009